**REMARKS**

Claims 1, 2, 5-8 and 26, and 35-38 are currently under examination. The Examiner has set forth several rejections which are addressed in the order outlined below:

I. Claims 1, 2, 5-6, 8, 26, and 35-38 are rejected under 35 USC § 101 as allegedly being directed to non-statutory subject matter.

II. Claims 1, 5-6, and 8 are rejected under 35 USC § 112, first paragraph, as allegedly lacking enablement.

**I. The Claims Are Directed To Statutory Matter**

The Examiner states that:

> ... the method is an experimental algorithm designed to identify further natural relationships ...

*Office Action, pg 3 ¶ 6.* The Applicants disagree that the pending claims allegedly violate 35 U.S.C. § 101 because the Examiner has misinterpreted the meaning of the statute. The Applicants do not present an entire method defining an experimental algorithm. The Federal Circuit has held that mathematical algorithms involving other statutory classes (i.e., devices or compositions of matter) are proper statutory matter. *See, State Street Bank & Trust Co. v. Signature Financial Group Inc., 149 F.3d 1368, 47 USPQ2d 1596 (Fed. Cir. 1998)*(holding that a mathematical algorithm performed on a device was patentable). In this case, the Applicant presents other steps, for example, "providing a nucleic acid", which are clearly within the statute as a composition of matter. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claims 1 and 26 to remove the "correlating" step for other reasons as explained below. This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

The Applicants respectfully request that the Examiner withdraw the present rejection.

**II. The Claims Are Enabled**

The Examiner states that the claims are allegedly not enabled:

> ... for a method of identifying individuals predisposed to schizophrenia by "detecting the presence of at least one polymorphism ... of said alpha 7 allele ... [and] ... any of the other variants as indicators that a human subject is predisposed to schizophrenia.

*Office Action pg. 4* ¶ 7. The Applicants disagree because the Examiner has apparently not made a complete review of the Applicants' specification by stating that:

> ... a physician cannot predict whether a patient is predisposed to schizophrenia, except where the C to T –86 variant is present. It is a well-known fact that physicians cannot predict that a person is predisposed to a disease, and in particular schizophrenia.

*Office Action, pg 5* [emphasis added]. The Examiner is respectfully requested to review Table 7 & Table 8 in the Applicant's specification (*See, pp 111 & 112*). Specifically, these data show that a large number of promoter polymorphisms that are more prevalent in schizophrenic patients and, therefore, do represent predisposition factors.

For example, the data in Table 7 show single promoter variants occurring more frequently in schizophrenic patients including, but not limited to: -86C/T; -92G/A, -143 G/A; –178 –G; -180 G/C; -191 G/A; -194 G/C; and -241 A/G. Overall, the data in Table 7 show that single promoter polymorphisms have a greater frequency in schizophrenic patients (36.4%) as compared to control subjects (28.5%).

Further, the data in Table 8 show dual promoter variants uniquely present in schizophrenic patients including, but not limited to: -46/-178; -146/-190; -46/-191; -86/-241; and -178/-191. Consequently, these dual promoter polymorphisms associated with the schizophrenic patients demonstrate predisposition factors operating at a 100% efficiency.

These data convincingly show that the present application has enabled a novel and unobvious approach to showing a predisposition to schizophrenia that has not been predicted in the art:

> Thus, polymorphisms in the core promoter of the full-length α7 nicotinic receptor gene are found more frequently in schizophrenic individuals than in subjects with no family history of schizophrenia, and double variants are likely to result from inheritance of one mutant allele from each parent.

*Applicants' Specification, pg 113 ln 30-31 – pg 114 ln 1-2* [emphasis added]. In fact, the Examiner's admission above that "physicians cannot predict that a person is predisposed to … schizophrenia" speaks resoundly to the novelty and non-obviousness of the Applicants' claimed embodiments. More to the point, the Examiner has presented a totally conclusory argument and is improperly speaking as one having ordinary skill in the art. An Examiner is required to provide evidence for such conclusions, by either pointing to specific publications or affidavit.[1] The Examiner has done neither.

In light of the Applicants' data, the Applicants have amended the claims accordingly (*infra*). The Applicants continue to recognize the prior species election to the –86 C/T variant, but believe the Examiner will find this variant patentable, thereby allowing eventual examination of, and allowance of, the newly presented Markush groups regarding all the enabled polymorphisms.

Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claim 1 to recite "a method of diagnosing schizophrenia", that comprise a "a physician's interview, wherein the subject presents at least one symptom of schizophrenia", and that the interview "differentiates schizophrenia from other forms of illness" for which the Examiner had previously indicated allowability (i.e., Claims 7 & 8). The Applicants discuss schizophrenia symptoms at length in the specification, for example:

> The term "schizophrenia" as used herein refers to a major mental disorder featuring psychotic symptoms during some phase of the illness, a long term course and a deterioration in function. Schizophrenic symptoms can be classified as positive, negative, cognitive and mood symptoms, which together or separately may result in behavioral disturbances (e.g., bizarre, apparently purposeless and stereotyped activity or inactivity).

[1] *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) ("[T]he examiner's assumptions do not constitute the disclosure of the prior art.").

*Applicants' Specification, pg 76 ln 8-12.* Based upon the many examples of polymorphisms showing a predisposition to schizophrenia, Claim 26 is amended to recite that a polymorphism within "SEQ ID NO:125" is sufficient to identify "that said subject is predisposed to schizophrenia". Consequently, Claims 7, 8, 37, & 38 are concomitantly canceled. In order to provide clarity to this embodiment, the phrases "the presence of" and "reduced transcription" have been deleted. Further, the step of "correlating ... with a predisposition to schizophrenia" step has been replaced with a previously allowable reference to a physician interview. *See, Applicants' Specification pg 77 ln 4-7.* These amendments are made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

In light of the above enablement argument the Applicants now present new Claims 39-46 directed to the many disclosed α7 polymorphisms linked to a subject's predisposition to schizophrenia. Single and dual polymorphisms dependent upon Claim 1 are conveniently separated into new Claims 45 & 46, and similarly new Claims 40 and 41 are dependent upon Claim 26.

New Claims 42 – 44 also provide an alternative embodiment for determining a subject's predisposition to schizophrenia by supplementation with P50 auditory response testing:

> Elevated P50 ratios were defined as values greater than or equal to 0.50, which were found in 91% of the unrelated schizophrenics and 6% of the normals.

*Applicants' Specification, pg 102 ln 1-3.* This embodiment exemplifies that the Examiner's above conclusory statement that:

> It is a well-known fact that physicians cannot predict that a person is predisposed to a disease, and in particular schizophrenia.

*Office Action, pg 5,* is contradicted by the Applicants' Specification, for example:

> As is described in more detail in Examples 11-16, the inventors provide evidence that functional polymorphisms in the promoter region of the α7 neuronal nicotinic acetylcholine receptor subunit gene (CHRNA 7 or α7), a candidate gene in the 15q13-

> q14 linkage region, were more frequently found in schizophrenic patients and were associated with a sensory deficit found in this common mental illness.

*Applicants' Specification, pg 30 ln 24-29,* and

> This P50 inhibitory deficit is inherited in families of schizophrenic patients in an apparently autosomal dominant pattern (Freedman et al., Proc Natl Acad Sci USA, 94:587-592, 1997; Freedman et al., Somat Cell Mol Genet, 13:479-484, 1987; and Clementz et al, Am J Psychiatry, 155:1691-1694, 1998). Thus, half of family members have aberrant gating of the P50 auditory evoked potential, whether or not they have the disease. The increased incidence in schizophrenic patients and their families indicates that the P50 deficit represents a trait that predisposes to schizophrenia.

*Applicants' Specification, pg 30 ln 24-29* [emphasis added]. This teaching from the Applicants' specification provides clear evidence that not only did those having ordinary skill in the art believe that is was possible to predict the occurrence of schizophrenia, but the Applicants have provided adequate guidance to perform such predictions.

The Applicants respectfully request that the Examiner withdraw the present rejection.

## CONCLUSION

Applicants believe the amendments and arguments set forth above traverse the Examiner's rejections and, therefore request that a timely Notice of Allowance be issued in this case. However, should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect.

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